Symposium: Interactions of Diet and Nutrition with Genetic Susceptibility in Cancer

Diet, Genetic Susceptibility and Human Cancer Etiology[1]

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ABSTRACT There is evidence that high penetrance hereditary genes cause a number of relatively uncommon tumors in the familial setting, whereas common cancers are influenced by multiple loci that alter susceptibility to cancer and other conditions. The latter category of genes are involved in the metabolism of carcinogens (activation, detoxification) as well as those that interact with dietary exposure. This paper will consider some of the basic principles in studying susceptibility genes and provide a few examples in which they interact with dietary components. J. Nutr. 129: 556S–559S, 1999.

KEY WORDS: • *heterocyclic amines* • *cytochrome P4501A2* • *N-acetyltransferase* • *MeIQx* • *genotype* • *phenotype* • *inducible*

The role of genetics in cancer etiology can be loosely grouped into the following two categories: the single (rare) genes and the more common susceptibility genes (**Table 1**). The high penetrance disease genes are uncommon (i.e., have a low allele frequency, typically less, or much less than 1%). When present, they confer a high relative and absolute risk of a particular cancer. Over a dozen genes have been identified and studied in the family setting (Vogelstein and Kinzler 1998). These include Rb (retinoblastoma), WT1 (Wilms tumor) and p53 (Li-Fraumeni syndrome). The second type is comprised of the more common, low penetrance genes thought to play a role in many or even most human diseases. These genes are characterized by a high gene frequency (1–90% or more), low relative and absolute risk, but potentially high population attributable risk. The role of exposure is critical for the susceptibility genes but may be only modest for the single gene (Caporaso and Goldstein 1996). In the majority of cases in which diet is involved in the carcinogenic process, it is the susceptibility genes that are thought to be most relevant (Sinha and Potter 1997).

Although a complete inventory of all of the processes that contribute to carcinogenesis remains to be elucidated, certain pathways unquestionably contribute to neoplastic transformation. Historically, early studies established that carcinogens require metabolic activation, and it was proposed that genetic control of activation (Ayesh et al. 1984, Kellermann et al. 1973) or elimination (Lower et al. 1979, Seidegard et al. 1986) might account for genetically mediated variation in tobacco- and diet-related cancer susceptibility. A broader appreciation of human carcinogenesis suggests categories of genes that go beyond metabolic activation/detoxification. These include genes that influence DNA repair, chromosome stability, the activity of oncogene or tumor suppressor genes, cell cycle control or signal transduction, hormonal or vitamin metabolism pathways, immune function and receptor or neurotransmitter action. In this paper, we will give some examples of genetic polymorphisms that may interact with various dietary components and thus define subgroups of individuals who may be at a higher risk of getting cancer.

Various xenobiotics, including dietary components, are metabolized by various hepatic and extrahepatic enzymes during the course of metabolism (**Fig. 1**). Phase I enzymes are generally involved in activating steps in the liver. Phase II enzymes facilitate the attachment of polar groups to increase water solubility and thereby facilitate elimination. Occasionally, this step can render compounds into more potent mutagens and carcinogens rather than detoxify. The process of activation by a phase I enzyme, cytochrome P4501A2 (CYP1A2),[3] and a phase II enzyme, N-acetyltransferase 2 (NAT2), is hypothesized for heterocyclic amines (HCA), a group of compounds found in meats cooked at high temperature (see below).

Figure 1 outlines the areas in which various dietary components may play a role in the activation/elimination pathway. Dietary components can be procarcinogens that can be activated by the phase I and II enzymes, e.g., HCA, polycyclic

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[3] Abbreviations used: ADH, alcohol dehydrogenase; CYP1A2, cytochrome P4501A2; DiMeIQx, 2-amino-3,4,8-trimethylimidazo(4,5-f)quinoxaline; EPHX, epoxide hydroxylase; GST, glutathione-S-transferase; HCA, heterocyclic amines; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline; MTHFR, metheylenetetrahydrofolate reductase; NAT2, *N*-acetyltransferase 2; PAH, polycyclic aromatic hydrocarbons; PhIP, 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine.

TABLE 1

Genes: single and susceptibility

Factor	Single	Susceptibility
Gene frequency	Rare	Common (>1%)
Study setting	Family	Population
Study type	Linkage	Association
Absolute/relative risk	High	Low
Attributable risk	Low	High
Role of environment	Modest	Critical

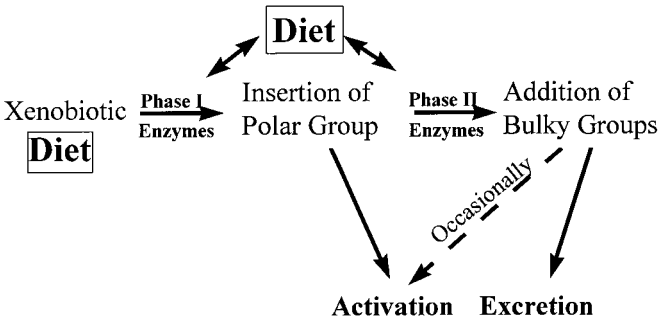

FIGURE 1 Pharmacogenetics of chemical carcinogenesis.

aromatic hydrocarbon (PAH) and aflatoxins. Furthermore, these procarcinogens and other dietary components can themselves influence the various phase I and II enzymes by induction or inhibition. CYP1A2 (phase I) activity can be induced by indole-3-carbinol, tobacco smoke, well-done meat, PAH in grilled and smoked foods, and inhibited by naringenin in grapefruit. Similarly, the phase II enzyme, glutathione-S-transferase (GST) can be induced by many nonnutrient phytochemicals (e.g., isothiocynates or dithiolthiones), dietary lipids and reactive oxygen species.

There are also other polymorphic enzymes that may interact with various dietary components and play a role in human carcinogenesis. Categories of susceptibility genes, potential dietary carcinogens and anticarcinogens, and cancer sites in which they may be involved are outlined in **Table 2**.

A few examples of dietary factors and genetic polymorphisms actively being investigated for colorectal cancers are outlined below. We will present the example of red meat and HCA consumption, CYP1A2 and NAT2 phenotype in relation to the risk of colorectal adenomas. Some hypotheses under investigation in which there may be interaction between dietary components and genetic polymorphisms are alcohol intake and the role of alcohol dehydrogenase (ADH) polymorphism, calcium intake, circulating vitamin D metabolite levels and polymorphisms in the vitamin D receptor. The relationship between folate and methionine status, and metheylenetetrahydrofolate reductase (MTHFR) polymorphism and its relation with colon cancer will be reviewed in a separate paper in this supplement. In each of the four examples, the dietary factors being investigated are risk factors for colorectal cancer. The polymorphic genes related to the metabolism of these dietary components are therefore potential candidates for future research. This type of approach has provided a mechanism-based rationale for research in this emerging field.

RED MEAT, HCA, CYP1A2 AND NAT2

Red meat or meat cooking methods such as frying and doneness levels have been associated with the increased risk of colorectal and other cancers (American Institute for Cancer Research 1997). It is not clear whether it is red meat intake or the way meat is cooked that is involved in the etiology of colorectal cancer. Both cooking methods and doneness level of red meat are thought to be surrogates for HCA consumption. The cancer risk to humans posed by HCA in the diet may also depend upon the extent to which these compounds are activated in vivo (Degawa et al. 1989). The initial activation step is thought to be *N*-oxidation by liver CYP1A2 (Turesky et al. 1991). The *N*-hydroxy arylamine metabolite is *O*-acetylated in the liver or transported to the appropriate target organ where it is *O*-acetylated by the polymorphic *NAT2* to form an arylamine-DNA adduct. The excretion of caffeine metabolites in urine after caffeine consumption reflected the action of both of these enzymes (Butler et al. 1992). The measured phenotype can distinguish between slow and rapid *O*-acetylators and *N*-oxidizers. The role of NAT2 (acetylation phenotype) in arylamine-related urinary bladder cancer has been evaluated in population studies that have implicated the slow acetylator phenotype as a risk factor for this cancer (Lee et al. 1994). There is also evidence that rapid metabolizers for both NAT2 and CYP1A2 have increased susceptibility to colon cancers (Lang et al. 1994).

Within the general population, individuals exhibit substantial differences in the activity of both CYP1A2 and NAT2 (Sinha et al. 1994, Sinha and Caporaso 1997). The reasons for the variability of these two enzymes are different. For NAT2, the variability is primarily due to genetic variants that determine function (Sinha and Caporaso 1997), with environmental factors playing a minor role in the phenotype. In contrast,

TABLE 2

Polymorphic genes, dietary components and cancer: possible candidates

Dietary component	Polymorphic gene/phenotype[1]	Cancer site
Carcinogens		
Heterocyclic amines	NAT2, (NAT1), CYP1A2 (CYP1A1)	Colorectal, breast, other sites
Polycyclic hydrocarbons	CYP1A1, GSTM1	Gastrointestinal tract
Nitrosamines	CYP2E1	Nasophyrangeal, stomach
Aflatoxins	GSTM1, EPHX	Liver
Alcohol	ADH (ALDH, CYP2E1)	Colorectal, oral
Anticarcinogens		
Cruciferous vegetables	CYP1A2, GST	Colorectal, other sites
Fruits and vegetables	CYP1A2, GST	Many sites
Calcium/vitamin D	Vitamin D receptor	Colorectal, prostate
Retinoids	Retinoic acid receptor variant	Acute promylocytic Leukemia, skin, Head and neck, breast
Folate, methionine	MTHFR, Methionine Synthase	Colorectal, cervix

[1] Abbreviations used: NAT, *N*-acetyltminsferase; CYP, cytochrome p450; GST, glutathione-S-transferase; EPHX, epoxide hydrolase; ADH, alcohol dehydrogenase; MTHFR, metheylenetetrahydrofolate reductase.

both genetic and environmental factors are likely to be responsible for the variability in CYP1A2 (Sinha et al. 1994, Sinha and Caporaso 1997). Various environmental factors, such as smoking, or certain dietary components, e.g., cruciferous vegetables and polycyclic aromatic hydrocarbons (PAH), as well as HCA in meats cooked at high temperature are known to induce enzyme activity (Sinha et al. 1994). In spite of intense study and the identification of a few polymorphic variants of the CYP1A2 gene, a clear genetic source of the variability remains to be demonstrated (Nakajima et al. 1994).

In a case-control study of colorectal adenomas, we examined the relation of risk to both doneness and meat intake. We found an increased risk associated with red meat consumption but not with total or white meat intake. The increased risk was associated mainly with the consumption of well done/very well done red meat compared with rare/medium red meat. High temperature cooking methods were also associated with increased risk, particularly with red meat that was grilled or pan-fried. We also found that 2-amino-3,4,8-trimethylimidazo(4,5-f)quinoxaline (MeIQx), 2-amino-3,4,8-trimethylimidazo(4,5-f)quinoxaline (DiMeIQx), and 2-amino-1-methyl-6-phenlimidazo(4,5-b)pyridine (PhIP), three of the most abundant HCA, in well-done red meat were associated with increased risk of colorectal adenomas.

It is too early to evaluate the evidence for a role of genetic susceptibility in relation to these risk factors. Lang et al. (1994) observed that subjects who ate well done meat and had high activity of CYP1A2 and NAT2 had higher risk of colorectal adenomas and cancer. However, the number of subjects in this subset were very small. In our study, in which we obtained detailed information on meat cooking and could estimate HCA consumption, we observed a possible interaction ($P = 0.10$) between MeIQx and CYP1A2. High CYP1A2 activity appeared to increase risk of colorectal adenomas in people who consumed low levels of MeIQx but not in people who consumed high levels of this compound. However, the study had small numbers ($n = 146$; controls = 228). Larger studies are required in the future to clarify these preliminary findings.

CALCIUM, VITAMIN D AND VITAMIN D RECEPTOR POLYMORPHISM

Polymorphisms in the vitamin D receptor gene, in intron 8 (*Bsm1*), and in the 3' untranslated region [poly (A) microsatellite] have recently been linked to prostate cancer risk (Ingles et al. 1997, Taylor et al. 1996). Ingles and co-workers found that people with one long (A_{18}–A_{22}) region in the vitamin D receptor had a greater than fourfold increase in risk for prostate cancer compared with people with two short (A_{14}–A_{17}) regions. Taylor and co-workers (1996) found that individuals who were homozygote mutants at codon 352, *tt,* were at 60% reduced risk for prostate cancer compared with subjects with homozygotes wild type and heterozygotes, *TT* or *Tt.*

Vitamin D inhibits proliferation in colorectal epithelium, suppresses growth in a colorectal cell lines (Thomas et al. 1992) and may play a role in regulating the expression of genes and protein products implicated in apoptosis (James et al. 1996). Dietary and supplemental vitamin D has been related to reduced risks of colorectal cancer in several recent studies (Martinez et al. 1996, Pritchard et al. 1996), although its association with colorectal adenomas is less consistent (Boutron et al. 1996, Kampman et al. 1994). Many studies are currently investigating the role of circulating vitamin D metabolites and dietary calcium. Because the vitamin D receptor is involved in vitamin D and calcium metabolism, the vitamin D receptor polymorphisms may also be important for colorectal cancers.

Sunlight may play a role in colorectal carcinogenesis by stimulating endogeneous vitamin D production and thus regulating calcium absorption (Emerson and Weiss 1992, Garland and Garland 1980). Calcium has been shown to decrease carcinogen-induced colonic tumors in animal models and to reduce epithelial cell proliferation in persons taking supplemental calcium who are at high risk for colon cancer (Lipman and Newmark 1995, Rozen et al. 1989). However, epidemiologic studies on dietary calcium and risk of colorectal cancers or adenomas have been suggestive but inconclusive (Garland et al. 1985, Kampman et al. 1994, Martinez et al. 1996, Pritchard et al. 1996).

ALCOHOL AND ALCOHOL DEHYDROGENASE

Recently, an international panel of experts published a report *Food, Nutrition and the Prevention of Cancer: A Global Perspective* in which they concluded that there was "convincing" evidence of increased risk for mouth, pharynx, larynx, esophagus and liver cancers, and "probable" evidence of increased risk of colorectal and breast rectal cancers with higher intake of alcohol (American Institute for Cancer Research 1997). Different mechanisms may be involved in the carcinogenic effect of alcohol, including induction of microsomal enzymes involved in the conversion of procarcinogens to carcinogens (Seitz et al. 1981). An indirect effect of alcohol consumption could be mediated through associated deficiencies of other nutrients such as folate, iron, zinc, riboflavin, pyridoxin and vitamin E (American Institute for Cancer Research 1997). The differential rate of ethanol metabolism due to genetic polymorphism in ADH may contribute to vulnerability to alcohol-related disease.

There are several ADH subtypes, with ADH type 3 (ADH_3) being polymorphic (Bosron et al. 1986, Harty et al. 1997). The enzyme encoded by the ADH_3^1 allele metabolizes ethanol to acetaldehyde 2.5 times faster than those encoded by the ADH_3^2 allele (Bosron et al. 1986). Most of the metabolism occurs in the liver (Li et al. 1986), but activity is also present in the oral cavity, as well as other parts of the digestive tract such as stomach, colon and rectum (Moreno et al. 1994, Seitz et al. 1996, Yin et al. 1994). Ethanol is primarily (80%) oxidized by ADH to acetaldehyde. In cell culture assays, acetaldehyde, but not ethanol, causes mutations and damage to the DNA (Grafstrom et al. 1994, Singh and Khan 1995), forms DNA-adducts both in vitro and in vivo (Fang et al. 1995), initiates transformation of kidney cells (Eker and Sanner 1986) and inhibits DNA repair (Grafstrom et al. 1994). These findings point to acetaldehyde as the carcinogen rather than ethanol itself. An epidemiologic study of oral cancer found substantially increased risk of ethanol-related oral cancer among subjects with $ADH_3^{1\text{-}1}$ genotype and very high alcohol consumption (Harty et al. 1997). Because epidemiologic studies of colorectal cancer have reported associations with alcohol, study of the interaction of ADH_3 polymorphism with this exposure may clarify the relationship.

Studies investigating the interactions between dietary exposure and genetic polymorphisms have the potential to clarify mechanisms and identify susceptible subgroups so that preventative strategies can be focused on the subgroups for maximum benefit. However, simulation of similar environmental exposure and genetic polymorphisms indicates that sample sizes may have to be in the thousands to have adequate power to examine these interactions (Rothman et al., in press). Many investigations of the role of diet and genetic polymorphisms

have examined very small numbers (in some cases <10) in the subgroup of interest. Future studies interested in investigating such hypotheses must both plan for much larger sample sizes and improve exposure assessment.

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